interest to generate analogs of peptide or protein antigens and co-stimulatory proteins for use within the invention.

Kindly replace the paragraph beginning at page 38, line 13 with the following new paragraph:

~~additional~~ *Additional* segments that provide for its transcription. As noted above, such additional segments include promoter and terminator sequences. DNA vectors for use within the invention also may include one or more origins of replication, one or more selectable markers, an enhancer, a polyadenylation signal, etc. Expression vectors generally are derived from plasmid or viral DNA, and can contain elements of both. The term "operably linked" indicates that the segments are arranged so that they function in concert for their intended purposes, for example, transcription initiates in the promoter and proceeds through the coding segment to the terminator (see, e.g., Sambrook et al., Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Laboratories, Cold Spring Harbor, N.Y., 1989, incorporated herein by reference).

REMARKS

The present restriction requirement sets forth the following groups of claims:

I. Claims 1-6 and 11-17, drawn to a method for eliciting an immune response comprising administering a tumor antigen and a non-viral vector encoding a T cell co-stimulatory molecule, classified in class 424, subclass 277.1 and class 514, subclasses 2 and 44.

II. Claims 1, 2 and 6-17, drawn to a method for eliciting an immune response comprising administering a viral antigen and a non-viral vector encoding a T

cell co-stimulatory molecule, classified in class 424, subclass 204.1 and class 514, subclasses 2 and 44.

III. Claims 18-22 and 27-31, drawn to an immuno-genic composition comprising a tumor antigen and a non-viral vector encoding a T cell co-stimulatory molecule, classified in Class 424, subclass 277.1 and class 514, subclasses 2 and 44.

IV. Claims 18, 19 and 23-31, drawn to an immunogenic composition comprising a viral antigen and non-viral vector encoding a T cell co-stimulatory molecule, classified in class 424, subclass 204.1 and class 514 subclasses 2 and 44.

Applicants elect to prosecute with traverse, Group II, claims 1, 2 and 6-17, wherein the claims are drawn to methods for eliciting an immune response comprising administering a viral antigen and a non-viral vector encoding a T cell co-stimulatory molecule. Applicants reserve the right to file a divisional or related copending application to the subject matter claimed in the non-elected groups. Further, the Examiner has requested election of a single disclosed species of viral antigen and polynucleotide encoding a T cell co-stimulatory molecule, suggesting one of the disclosed species recited in claim 20 and one of the disclosed species recited in claim 27, to be used in the method of Group I for further prosecution to which claims would be restricted if no generic claim is finally held to be allowable. Applicants have also been requested to list all claims readable on the elected species including those claims subsequently added. No claims have been indicated by the Examiner as being generic.

Applicants elect with traverse as the species for substantive examination antigens that are viral antigens of HPV and as the T cell co-stimulatory molecule the molecule B7-1. In particular, the HPV E7 antigen is elected as the antigen for continued prosecution. Further, Applicants note that upon indication of allowability of a generic claim, a reasonable number of additional species will be considered and can also be

claimed in the same application as provided by 37 C.F.R. § 141. Claims 1, 2, 6-8, and 11-17 are believed to be readable on the elected species. Claims 1 and 6 are generic.

It is respectfully requested that the Examiner reconsider the present request for restriction in order that Applicants might be allowed a compact and expedited prosecution of the present invention and to provide a patent which adequately protects the entire invention.

Restriction can be required by the Office for certain reasons as set forth in the MPEP under section 800. Such restriction is entirely at the discretion of the Office. Restriction is required so that an undue burden is not placed on the Office in prosecuting the application, so that the statutory fee structure is not subverted, and so that the integrity of the examination and classification system of the Office are not jeopardized. Requirement for restriction is balanced against the right of the Applicants to claim their invention as they require to adequately protect their invention and to provide for a compact and expedited prosecution.

Applicants submit that these criteria are not met by the restriction request for present application. The present invention relates to methods and compositions for inducing an immune response in a subject comprising administering an immunologically effective amount of a peptide or protein antigen costimulatory molecule. Coordinately with a non-viral vector comprising of polynucleotide encoding a T cell. Peptides and protein antigens of the invention must comprise on or more T cell epitopes. In particular, the T cell epitopes are T helper cell epitopes and/or cytotoxic T cell epitopes capable of electing a specific T cell response in the subject. These epitopes are well defined and are present in antigens from many sources including tumor antigens and viral antigen that differ considerably in their source and structure. The immune response to these peptides and protein antigens that combine a T cell epitope(s) in the subject is improved by the co-administration of a non-viral vector comprising of polynucleotide encoding a T cell co-stimulatory molecule. Because these methods and compositions comprise a single inventive concept that can not be prosecuted in a form commensurate with the entire

scope of the claimed invention. Applicants believe they properly constitute a single invention not requiring restriction.

Also, as Applicants believe the present invention as claimed comprises a single inventive concept, any search of the patent or scientific literature directed to methods or immunogenic composition as claimed would be expected to encompass at in the field of the invention as claimed. It should be further noted that each of the groups as set forth by the Examiner are classified in at least on common class and even subclass. Thus, prosecution of the invention as a whole should not place a burden on the Examiner sufficient to justify restriction nor the loss of Applicants ability to claim the entire invention. Therefore, Applicants respectfully request that the Examiner reconsider this request for restriction.

Further, should the Examiner believe restriction to be proper, Applicants request consideration of examining the claims of Group II and Group IV together. Consideration of these claims together would allow substantive examination of methods and compositions for use in those method to be examined together.

Also, Applicants have reviewed the claims and the specification for errors. Several typographical and clerical errors have been corrected above as set forth in the section entitled "in the Specification" and in the attached appendix. All amendments to the specification are to correct obvious typographical and clerical errors and no new matter has been added by any amendment described herein.

CONCLUSION

In view of the foregoing, Applicants have elected with traverse Group II, claims 1, 2 and 6-17 and also elected viral antigen, i.e., E7, and a non-viral vector comprising the polynucleotide encoding the T cell co-stimulatory molecule B7-1. Reconsideration of the request for restriction is respectfully requested for the reasons set forth above. Should the Examiner retain this request Applicants respectfully request substantive examination of the claims encompassed by Groups II and IV to allow the

simultaneous consideration of methods and compositions used in the method. Applicants believe all claims now pending in this application are in condition for allowance. The issuance of a formal Notice of Allowance at an earlier date is respectfully requested. if for any reason the Examiner believe that a teleconference would expedite prosecution of the subject application, the Examiner is invited to telephone the under signed at 206-467-9600.

Respectfully submitted,

Dated: 16 October 2002

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APPENDIX

VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE SPECIFICATION:

Please delete the paragraph beginning at page 3, line 8, and replace with the following paragraph:

Another mechanism that may contribute to the inefficient induction of tumor-reactive T cells is suggested by the "two-signal" model for lymphocyte activation. This model was originally proposed for B lymphocytes (Bretscher and Cohn, Science 169:1042-1049, 1970, incorporated herein by reference) and later as an explanation for why antigens expressed on cells of ~~nonhematopoetic~~ ***nonhemotpoietic*** origin are ineffective at inducing transplant rejection (Lafferty et al., Ann. Rev. Immunol. 1:143-173, 1983, incorporated herein by reference). A two-signal model has now been proposed for all lymphocytes (Janeway, C.A., Jr., Cold Spring Harbor Quant. Biol. 54:1-13, 1989; Nossal, G. J. V., Science 245:147-153, 1989; and Schwartz, Cell 57:1073-1081, 1989, each incorporated herein by reference). According to this model, optimal stimulation and effective antigen-specific clonal expansion of lymphocytes require both a primary, antigen-specific signal, and a secondary, "co-stimulation" signal.

Please delete the paragraph beginning at page 7, line 3, and replace with the following paragraph:

In alternative aspects of the invention, the peptide or protein antigen may incorporate a T cell epitope of a tumor antigen or antigen of a viral or non-viral pathogen. In more detailed aspects, the peptide or protein antigen incorporates an epitope from a tumor antigen, for example the proteins (or products encoded by) p53, *ras*, *rb*, *mcc*, *apc*, *dcc*, *nfl*, VHL, MEN1, MEN2, MLM, Her-2neu, CEA, PSA, Muc1, Gp100, tyrosinase, and MART1. Alternatively, the peptide or protein antigen may comprise an epitope of a

viral antigen, for example an antigen of human immunodeficiency virus (HIV), hepatitis B virus (HBV), hepatitis C virus ~~(HBC)~~ ***(HCV)***, herpes simplex virus (HSV) or human papilloma virus (HPV).

Please delete the paragraph beginning at page 13, line 13, and replace with the following paragraph:

Therefore, mutant *ras* peptides serve as particularly useful vaccine agents to elicit anti-cancer immune responses according to the methods of the invention. In this context, *Ras* p21 is an intracellular protein subject to ~~antigenprocessing~~ ***antigen processing*** and presentation by MHC molecules. Specific CD4+ and CD8+ T lymphocytes that can recognize a single *ras* mutation have been described. Murine experiments have shown that T lymphocytes specifically immunoreactive against mutated *ras* peptides have the ability to lyse target cells that endogenously express the same point mutated *ras* gene. These lytic T cells display cytotoxic activity of both CD4+ (Th1 subtype) and CD8+ subsets (Abrams et al., Eur. J. Immunol. 25:2588-2597, 1995; Peace et al., J. Immunother. 14:110-114, 1993; Peace et al., J. Exp. Med. 179:473-479, 1994; and Skipper et al., J. Exp. Med. 177:1493-1498, 1993, each incorporated herein by reference). Furthermore, induction of anti-*Ras* CTLs by vaccinating mice with recombinant mutant *ras* proteins has led to the rejection of syngeneic tumor cells bearing the corresponding mutation (Fenton et al., J. Natl. Cancer Inst. 85:1294-1302, 1993, incorporated herein by reference).

Please delete the paragraph beginning on page 19, line 8 and replace with the following paragraph:

Additional HIV peptide antigens (designated by source protein/amino acid sequence/and position) for use within the invention include P21 (~~gp120~~ ***gp120***/QIDSKLREQFGNNK/410-429) (SEQ ID NO. 38); (gp120/GSDTITLPCRIKQFINMWQE/644-658) (SEQ ID NO. 39); P41 (gp41/NYTSLIHSLIEESQN/664-678) (SEQ ID NO. 40); P42

(gp41/EQELLELDKWASLWN/787-801) (SEQ ID NO. 41); P47 (gp41/RIVELLGRRGWEALK/172-196) (SEQ ID NO. 42); (pol(rt)/IETVPVKLKPGMDGPKVKQWPLTEE/325-349) (SEQ ID NO. 43); (pol(rt)/AIFQSSMTKILEPFRKQNPDIVIYQ/342-366) (SEQ ID NO. 44); (pol(rt)/NPDIVIYQYMDDLYVGSDLEIGQHR/359-383) (SEQ ID NO. 45); (pol(rt)/DLEIGQHRTKIEELRQHLLRWGLTT/461-485) (SEQ ID NO.46); (pol(rt)/PLTEEAELELAENREILKEPVHGVY/495-519) (SEQ ID NO. 47); and (pol(rt)/EIQKQGQGQWTYQIYQEPFKNLKTG/265-279) (SEQ ID NO. 48) (Sequence numbers for gp120 and gp41 are from Ratner et al., Nature 313:277-284, 1985, and sequence numbers for pol and gag proteins from Sciliciano et al., Cell 54:561, 1988, and Walker et al., Proc. Natl. Acad. Sci. USA 86:9514, each incorporated herein by reference).

Please delete the paragraph beginning at page 30, line 16, and replace with the following paragraph:

Analogs of peptide or protein antigens and co-stimulatory proteins may be readily constructed, e.g., using peptide synthetic techniques well known in the art such as solid phase peptide synthesis (~~Merrifield~~ ***Merrifield*** synthesis) and the like, or by recombinant DNA techniques well known in the art. Techniques for making substitution mutations at predetermined sites in DNA include for example M13 mutagenesis. Manipulation of DNA sequences to produce substitutional, insertional, or deletional variants are conveniently described elsewhere such as Sambrook et al., 1989, *supra.* In accordance with these and related teachings, defined mutations can be introduced into a native peptide or protein antigen or co-stimulatory protein to generate analogs of interest by a variety of conventional techniques, e.g., site-directed mutagenesis of a cDNA copy of the peptide or protein antigen or co-stimulatory protein. This can be achieved through and intermediate of single-stranded form, such as using the MUTA-gen® kit of Bio-Rad Laboratories (Richmond, CA), or a method using the double-stranded plasmid directly as a template such as the Chameleon® mutagenesis kit of Strategene (La Jolla, CA), or by the polymerase chain reaction employing either an oligonucleotide primer or a template

which contains the mutation(s) of interest. A mutated subfragment can then be assembled into a complete analog-encoding cDNA. A variety of other mutagenesis techniques are known and can be routinely adapted for use in producing the mutations of interest to generate analogs of peptide or protein antigens and co-stimulatory proteins for use within the invention.

Please delete the paragraph beginning at page 38, line 13, and replace with the following paragraph:

~~additional~~ ***Additional*** segments that provide for its transcription. As noted above, such additional segments include promoter and terminator sequences. DNA vectors for use within the invention also may include one or more origins of replication, one or more selectable markers, an enhancer, a polyadenylation signal, etc. Expression vectors generally are derived from plasmid or viral DNA, and can contain elements of both. The term "operably linked" indicates that the segments are arranged so that they function in concert for their intended purposes, for example, transcription initiates in the promoter and proceeds through the coding segment to the terminator (see, e.g., Sambrook et al., Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Laboratories, Cold Spring Harbor, N.Y., 1989, incorporated herein by reference).